12. HEALTH RISK CHARACTERIZATION FOR DIESEL ENGINE EMISSIONS

12.1. INTRODUCTION

12.1.1. Scope

Earlier chapters focused on specific risk assessment topics and developed key findings for these topics or provided an overview of relevant background information. This chapter will integrate and summarize the key findings about the health hazards and risk potential for humans exposed to diesel exhaust (DE). This chapter will first integrate the key information and pertinent uncertainties for two of the three basic components of risk assessment: hazard identification and dose-response assessment. Exposure assessment, the other basic component, is not in the scope of this report, though an exposure perspective is included as background information. The final section will characterize the hazards and risk in a plain-language summary form.

For introductory purposes, a quick overview of findings in the key assessment areas will help put the remainder of this chapter into perspective.

- The DE particle and its coating of organics, as well as the accompanying gases and semivolatiles, have biochemical and toxicological properties that raise a suspicion about adverse health effects given sufficient exposure. Because DE is found only as a mixture, the choice of dosimeter for measuring exposure is an important issue. For DE, $\mu g/m^3$ of diesel particulate matter is used.
- Carcinogenicity: Epidemiologic data are strongly suggestive of a carcinogenic hazard to the lung under occupational exposure conditions. Some rat and mouse studies show a similar effect at high test exposures. Mode-of-action information poses the challenge of sorting among high-dose particle effects and possible low-dose effects from mutagenic/genotoxic organics.
- Noncancer toxicity: For chronic exposure, there is limited human and much animal evidence for adverse respiratory effects, such as airway restriction, other measures of reduced pulmonary function, and immunologic allergenic reactions. Acute exposure in humans elicits various reactions from some individuals, ranging from annoying or temporarily debilitating symptoms reflecting tissue irritation, up to permanent harm to the respiratory system from very high acute exposure episodes.
- Ambient exposures to DE vary widely depending on whether an occupational element is involved, the setting is urban or rural, or near to or distant from a source of DE emissions. General average ambient exposures run in the 0.6 - 3.2 $\mu g/m^3$ (of particulate) range, though some areas can be in the 4-22 $\mu g/m^3$ range at certain periods during the year.

12.1.2. What Is Diesel Exhaust in a Risk Assessment Context?

As reviewed in more detail in Chapter 2 and other chapters, a health risk characterization for DE is more complicated than for most environmental pollutants because DE is a complex mixture. The mixture consists of particulate matter made up of an elemental carbon core with hundreds of compounds adsorbed to the surface (particle-phase emissions) and a volatile fraction that is also made up of many organic and inorganic compounds (gaseous-phase emissions). The particles, the particle coating of adsorbed compounds, and the volatile elements each have known properties from which hazards can be inferred, in addition to the aggregate hazard potential posed by the whole mixture.

The exhaust particles are formed through the condensation of even smaller particles in the engine and engine exhaust pathway. They average about 0.2 µm in diameter and have a very large surface area (50-200 m^2/gm). The main constituent is carbon, which accounts for approximately 80% of total particle mass. Approximately 70% of the total carbon occurs in the form of elemental carbon, the remainder being various organic compounds, called organic carbon. The particle constituents coating the particle surface include inorganics and hundreds of hydrocarbons. At least 16 hydrocarbons adsorbed onto the particles have been classified as having a carcinogenic potential for humans. Many of the compounds emitted as gases are potentially carcinogenic or otherwise toxic at some dose. These include benzene, 1,3-butadiene, various aldehydes, ethylene dibromide, nitroaromatics, oxides of nitrogen, and sulfur compounds. Additionally, there is evidence that reactive oxygen or hydroxal species (free radicals) may be formed on the particle surface that could cause or exacerbate damage to biological cells. Inorganic compounds are also present, including nitrates and compounds of sulfur.

The quantitative physical-chemical composition of DE exhaust is variable and depends on numerous factors, including operating conditions, heavy-duty versus light-duty engines, engine design, engine age, fuel technology, and exhaust control technology. Heavy-duty and off-road diesel engines have the largest U.S. particulate emissions. The human and animal health studies are pegged to specific engine exhaust generated at some time in the past, so the question of how relevant those exposures are to current conditions is a valid inquiry. There is no single answer to this question. However, health studies focus on particle mass as a surrogate for the DE mixture, so as the mass changes so may the applicability of the assessment findings.

Once diesel emissions are released in the air, they are subject to dispersal, dilution, and chemical and physical transformations. Newly emitted exhaust is “fresh” and has free radicals that pose some extra hazard, the magnitude of which is not discernable. DE that is more than a day old is “aged,” largely because of atmospheric alterations, and is thought to have fewer free radicals. The atmospheric alterations produce secondary pollutants that also have hazardous properties or potential toxicity. The formation of the secondary pollutants will vary depending on atmospheric conditions. A comprehensive assessment of the health risks posed by DE would also consider the risks posed by the atmospheric reaction products, a task that is not addressed in this assessment. Table 12-1 lists many of the particle-phase and gaseous-phase emissions in DE, as well as the atmospheric reaction products associated with each of these emissions.

12.2. HAZARD ASSESSMENT

Hazard assessment reviews what is known about the ability of DE to cause adverse effects (i.e., toxicity) in humans and laboratory animals and characterizes the likelihood that these effects are, in fact, human hazards. It also discusses the biological mechanisms that may be causing the toxicity and comments on the reliability and uncertainties of key studies.

12.2.1. Hazard Assessment for Health Effects Other Than Cancer

As reviewed in Chapter 5, exposure to diesel exhaust has been shown to induce a number of effects in humans and in experimental animals. As exposure progresses from episodic to more frequent, from shorter and longer duration, or from small to large concentrations, the evidence shows that symptoms progress from being annoying to being more temporarily disabling and become more severe, with increasing likelihood of permanent damage at high enough or long enough exposure. Although this section sets the stage for drawing conclusions about the potential for hazard, quantitative evaluations to estimate acceptable exposure levels are discussed in Chapter 6, the Inhalation Reference Concentration section.

12.2.1.1. *Effects From Acute Exposure*

The most readily identified acute noncancer health effect of DE on humans is its ability to elicit complaints of eye, throat, and bronchial irritation as well as physiological symptoms such as headache, lightheadedness, nausea, vomiting, and numbness and tingling of the extremities. Such symptoms have been reported by individuals exposed to DE on busy city streets or in bus stations. Recent human and animal studies also show that acute DE exposure episodes play a role in the development of allergic disease (immunological allergic reactions), resulting in prolonged hypersensitivity to DE and perhaps other ambient contaminants. We do not know what DE concentrations, per se, induce allergic responses, though particle concentrations of 10^6 per cm^3 induced symptoms of eye and nasal irritation and airway resistance in one study.

Acute animal studies have also shown that the gaseous components of DE elicit toxic responses. These include NO_2 (lung damage) and aliphatic aldehydes (irritation). Other animal evidence shows that acute exposure to high enough concentrations of whole DE does cause lung damage. In laboratory animals acutely exposed to high concentrations of whole DE, pulmonary edema (an excessive accumulation of fluid) often occurs during the first few days of exposure. After several days, aggregations of particle-laden macrophages have been observed in the

Table 12-1. Particle-phase and gaseous-phase emissions from diesel exhaust and their atmospheric reaction products

Emission component	Atmospheric reaction products
Particle-phase emissions	
Elemental carbon	—
Inorganic sulfate	—
Hydrocarbons (C_{14}-C_{35})	Little information; possibly aldehydes, ketones, and alkyl nitrates
PAHs ($\geq$4 rings) (e.g., pyrene, benzo[*a*]pyrene)	Nitro-PAHs ($\geq$4 rings); nitro-PAH lactones
Nitro-PAHs ($\geq$3 rings) (e.g., nitropyrenes)	Hydroxylated nitro derivatives
Gaseous-phase emissions	
Carbon dioxide	—
Carbon monoxide	—
Oxides of nitrogen	Nitric acid, ozone
Sulfur dioxide	Sulfuric acid
Hydrocarbons	
Alkanes ($\leq C_{18}$)	Aldehydes, alkyl nitrates, ketones
Alkenes ($\leq C_4$) (e.g., 1,3-butadiene)	Aldehydes, ketones
Aldehydes	
Formaldehyde	Carbon monoxide, hydroperoxyl radicals
Higher aldehydes (e.g., acrolein)	Peroxyacyl nitrates
Monocyclic aromatic compounds (e.g., benzene, toluene)	Hydroxylated and hydroxylated-nitro derivatives
PAHs ($\leq$4 rings) (e.g., phenanthrene, fluoranthene)	Nitro-PAHs ($\leq$4 rings)
Nitro-PAHs (2 and 3 rings) (e.g., nitronaphthalenes)	Quinones and hydroxylated-nitro derivatives

Source: Health Effects Institute (1995).

alveolar regions of the lungs. At the same time, a proliferation of cuboidal type II alveolar cells is observed, replacing thinner type I cells and thickening the alveolar walls. Because of the key role alveoli play in the exchange of gases, these changes may inhibit the efficiency of pulmonary function. Human studies are inadequate to evaluate potential toxic effects resulting from acute exposures.

The observed effects from single high-dose or episodic exposures in test animals are consistent with effects seen with lower and more long-term exposures. This suggests that total accumulated dose may be one basis for characterizing DE hazards, but this could be too simplistic for all aspects of DE toxicity because dose-rate aspects cannot be ruled out.

12.2.1.2. *Effects From Short-Term and Chronic Exposure*

Based on suggestive evidence from human occupational studies, combined with multiple controlled laboratory animal studies in several species, a high level of confidence exists that chronic exposure to DE constitutes a noncancer respiratory hazard for humans. As DE exposure levels and duration increase, the onset of respiratory symptoms in humans is observable on a limited basis, whereas in animal studies the onset of symptoms is more clear and replicable. Current data do not support confident identification of health hazards other than for the respiratory system. Chapter 5 discusses this topic in more depth.

Several studies of workers occupationally exposed to DE on a short-term basis have monitored pulmonary function at the beginning and end of work shifts to see if this marker of respiratory distress has been impaired by exposures. Short-term symptoms are seen (e.g., bus garage workers experienced burning and watering of the eyes, coughing, labored breathing, chest tightness, and wheezing), but no reduction in pulmonary function. A study of stevedores showed an adverse effect on pulmonary function, but normal function returned a few days after DE exposure stopped. It was noted in one study that occupationally exposed smokers appeared to demonstrate larger work-shift respiratory function decrements and increased incidence of respiratory symptoms. Other occupational studies did not find statistically significant effects from short-term exposure, though these studies have limitations that reduce the ability to detect responses.

Noncancer effects of chronic DE exposure have also been evaluated in epidemiologic studies of occupationally exposed workers (metal and nonmetal miners, railroad yard workers, stevedores, and bus garage mechanics). Some of the data indicate an absence of increased respiratory disease associated with exposure. In a few studies, though, a higher prevalence of respiratory symptoms, primarily cough, phlegm, or chronic bronchitis, was observed among the exposed, but usually without significant changes in pulmonary function. However, two studies, one of stevedores and one of coal miners, detected statistically significant decrements in baseline pulmonary function consistent with obstructive airway disease, thus providing some suggestion that impairment of pulmonary function among occupational populations may be occurring. Recent investigations have also indicated that human exposure to DE may result in the development of immunologic-driven allergic hypersensitivity; this would be a new health concern for DE exposure.

Overall, these results are suggestive of adverse chronic effects for humans, but database limitations preclude drawing more definitive conclusions. The epidemiologic investigations suffer from methodological limitations that confound the observations and limit the assignment of these observations to DE exposure. The limitations include (1) incomplete information on the extent of exposure to DE, necessitating in some studies estimations of exposures from job titles and resultant misclassification; (2) the presence of confounding variables such as smoking or occupational exposures to other toxic substances (e.g., mine dusts); (3) the short duration and low intensity of exposure; and (4) unlike in animal experiments, pathological evaluation of human lung tissue is seldom available for confirmatory analysis.

The suggestive human experience, however, is reinforced by a considerable body of animal evidence that clearly correlates DE exposure with pulmonary injury. The combined human and animal data are sufficient to infer that this hazard likely exists for humans. Short-term animal exposures to DE containing high concentrations of particulate matter (PM) resulted in histological and cytological changes in the lungs, but only minimal effects on pulmonary function. A number of long-term laboratory studies with rats, mice, Chinese hamsters, Syrian golden hamsters, cats, and Cynomolgus monkeys found varying degrees of adverse lung pathology. Exposures for several months or longer to levels markedly above environmental ambient concentrations resulted in accumulation of particles in the animal lungs and an impaired ability to clear particulate matter from the lungs. Histological studies also showed a variety of changes in respiratory tract tissue, including focal thickening of the alveolar walls, replacement of Type I alveolar cells by type II cells, and fibrosis. Because these effects were seen in a wide range of animal species, there is a compelling basis to believe that humans would also be at hazard under some condition of exposure.

Respirable particles in general have been implicated as etiologic factors in various types of chronic human lung diseases (U.S. EPA, 1996). Ambient particulate matter (PM) is associated with increased morbidity and mortality, aggravation of respiratory and cardiovascular disease, changes in lung function and increased respiratory symptoms, changes to lung tissues and structure, and altered respiratory defense mechanisms. The effects vary as one considers “fine” particles (e.g., $PM_{2.5}$) compared with “coarse” particles (e.g., PM_{10}). The vast majority of DE particles are fine and ultrafine in size and thus contribute to ambient levels of $PM_{2.5}$. In addition, DE contributes significantly to total ambient PM. For instance, Yoshizumi (1989) indicated that for Tokyo, the yearly mean concentration of DE particles was about 40% of the total particle concentration.

Epidemiologic studies of the effects of DE on organ systems other than the pulmonary system are scant. Animal studies have suggested that liver and kidney changes may be occurring at high concentrations, along with some indication of neurotoxic effects. Impaired growth rates have also been observed in animals chronically exposed to DE. However, since these effects are only seen at relatively high exposure levels, this does not imply a hazard for humans at low ambient exposures.

12.2.2. Toxicity Mode of Action

An understanding of the mode of action(s) (MOA) for toxicity allows one to make informed choices about how to translate observed toxicity data into specific risk assessment guidance that protects human health. For example, MOA information may help answer several questions: (1) Are all humans equally susceptible or just some population subgroups? (2) Are animal responses predictive of potential human responses because the animal MOA is thought to operate in humans? (3) Are high-dose effects extrapolatable to low ambient levels of exposure, and what does the shape of the low dose-response curve look like? and (4) a number of other specific qualitative and quantitative matters. In the absence of convincing or reasonably clear MOA information, scientific inference or default assumptions based on science policy are used in order to facilitate risk assessment conclusions, if a hazard potential is suspected.

Chapters 7, 9, and 10 contain more in-depth review of the mode-of-action topic.

With DE being a mixture and having several distinct components, the topic of MOA(s) is complex. For the carbon core particle component of DE, the pathogenic sequence following the inhalation of the diesel particle begins when alveolar macrophages (AMs), “scavenger” cells that defend the lungs from invading foreign matter, ingest diesel particles. When AMs ingest particles in large numbers they are activated and release chemical signals that attract neutrophils (a component of white blood cells) and additional AMs. As the lung burden of diesel particulate matter increases, particle-laden AMs aggregate in alveoli adjacent to terminal bronchioles. The overloaded neutrophils and AMs produce and release compounds that mediate inflammation. The particle-laden macrophages also become less mobile, thus decreasing their ability to clear particles from the lung. The latter series of events may result in inflammation of the lung, with replacement of very thin type I alveolar cells with more cuboidal type II cells, slowing exchange of oxygen and carbon dioxide. Continued exposure may result in further consequences, such as lung fibrosis and/or emphysema. This mode of action has a dose threshold because at some point the normal detoxification mechanisms become overloaded and consequential toxicity ensues. This MOA may also contribute to a carcinogenic response as discussed below. At least in the rat, the particle-driven toxicity and carcinogenicity can be viewed as being driven by the elemental carbon particle or a combination of the physical particle and the accompanying organics, depending on how several types of studies are interpreted. Intratracheal instillation of unaltered DE particles gave a stronger carcinogenic response than particles stripped of the organics, suggesting that particle-associated compounds play a role in tumor induction. Inhaled pure carbon particles (printex), however, were as effective in the induction of lung tumors as DE. Printex has a larger surface area per unit mass than diesel particulate matter. An initial notion that organics play an insignificant role is not necessarily indicated, however, because the very large surface area of the printex, a factor known to be related to cancer potency, may well make up for its lack of surface-adhering organics. In fact, a recent study has shown that stripping the organics from the DE particulates reduced their carcinogenic potency. Several animal studies also show that filtered DE (e.g., the gases without the coated particles) is ineffective in producing lung tumors in rats.

As for the chemical compounds that coat the particles, mutagenicity and genotoxicity assays reveal activity for the intact coated particles as well as organics extracted from the particles. Some of the gaseous fractions of the DE mixture are also mutagenic. The correlation of mutagencity-genotoxicity with carcinogencity isn't rigid, but the presence of this activity gives rise to support for a carcinogenic hazard, as well as suggesting some possible modes of action for cancer.

The operable mode of action for toxicity of the DE mixture taken as a whole is not definitively known. There are likely to be several modes operating, given the many DE constituents. A simplistic combination of modes to consider might have the following elements: (1) DE organics at low or high doses can initiate DNA damage which, if particles were not present, would have a probability to advance to cancer as a function of increasing total dose. This would also be considered a likely nonthreshold process because of the mutagenic properties of many of the organics on the particles and in the gases, and by EPA preference would be modeled for extrapolation purposes with a linear model; (2) with particles also present that overload normal lung detoxification at higher exposures, the particles continue to deliver organics to the deep lung, resulting in an increased residence time for the organics. The particles also add a second and seemingly dominant MOA (at least in the rat model) that induces a particle-specific proliferation of cells (because of the inflammatory consequences of the particles), thus accelerating growth of any DNA-damaged cells; (3) the presence of particles, even at nonoverload levels, may also influence carcinogenicity by contributing to additional DNA damage via the free radicals present on the particle surface, which are potent oxidizing agents for bio-organic substrates.

The observation that some of the DE-induced rat tumors are different pathologically from what one would expect in humans and that some are similar may also support the thought that multiple MOAs may be present.

Given the information at hand, dual modes of action are more likely than a single mode. One would be driven by particles and one by the organic/inorganic components, with a shifting influence as the exposure/dose varies from high to low. The role of contributory toxicity from other constituents, such as NO_2 or oxygen free radicals, among others, is uncertain.

It would be ideal if the MOA were informative about whether all humans were equally susceptible or whether some population subgroups were more or less susceptible. The human evidence, i.e., occupational and population-derived studies, does not provide any particular insight about variations in susceptibility, nor do the animal studies. Neither female versus male nor adult versus children's susceptibility differences are specifically indicated: the former may have been discernable given the nature of the studies, but there is no study basis to address possible children's risk issues. Later, in this section, a qualitative discussion about susceptibility is included that acknowledges that toxicological wisdom suggests that background respiratory system conditions could make some in the population more susceptible to chronic effects of DE exposure. Similarly, infants and children could have greater susceptibility simply because their developing organs and defense systems may be less effective at dealing with insults from DE exposure. These suggestions are not unique to DE exposure, though.

12.2.3. Carcinogenic Hazard Assessment

For inhalation exposure, both human studies and animal bioassays are available to assess the chronic exposure carcinogenic potential for DE. In fact, both the human and the animal studies provide evidence that exposure to DE has potential to be carcinogenic to humans under some condition of exposure. Chapters 7 and 8 review these data in detail. A finding about the hazard potential does not specify the magnitude of the impact, information on which is discussed in Chapter 11, the carcinogenicity dose-response evaluation section.

12.2.3.1. *Human Evidence*

A total of 26 key epidemiologic studies have been evaluated to examine the association between exposure to DE and increased cancer response. The positive human evidence consists of observed increases in lung cancer mortality in a number of occupational exposure studies and some suggestion of other possible cancer sites. Cohort, case control, and population-based studies are available. Exposure is most often defined indirectly by occupation or job title in the industry-related studies and is self-reported in population-based studies. The lack of direct exposure measurements, a condition common to retrospective epidemiology studies, is an overall limitation in the database. An excess risk (e.g. elevated standardized mortality ratios, relative risks, or odds ratios >1.0) for lung cancer was observed in 5 of 9 cohort studies and 8 of 10 case-control studies.

Of these studies, three cohort and three case-control studies observed a dose-response relationship by using duration of employment as a surrogate for dose.

The most convincing evidence that exposure to DE can induce lung cancer in humans comes from case-control and cohort studies among U.S. railroad workers and truck drivers. The study of railroad workers, a well-conducted and well-analyzed study, is evaluated and published as both a cohort and case-control study with varied controlling for confounders. The case-control study is the best for control of confounders, especially the question of smoking and its possible role as a confounder for the reported lung cancer increase. Statistically significant higher risks of 41% to 43% for lung cancer were found in the case-control study for 20 or more years of exposure, and these risks were not confounded by smoking or asbestos exposure, adjustments for which were rigorously accounted for in the study methodology. In the retrospective cohort study of these same railroad workers, the risks varied from 20% to 72% higher than the general population, all statistically significant depending on the duration of exposure. Although adjustments for possible asbestos exposure were accounted for, there was no adjustment for the possible role of smoking. However, recognition was given to the rigorous smoking adjustments in the case-control study, which showed no effect on risks. Though the overall risks were increased in the railroad worker cohort study, the identification of a dose-response relationship is a subject of debate. A case-control study of truck drivers showed statistically significant increased risks of 80% to 240%, depending on data stratification and duration of exposure after adjustment for smoking.

There is a notable consistency in finding elevated, although not always statistically significant, increases in lung cancer among workers exposed to DE in several industries. There are industry-specific findings of elevated lung cancer risk from truck drivers, professional drivers, and railroad workers, with some of the studies having adjusted for smoking. When the possible role of smoking as a confounder was accounted for, the increased risks prevailed.

A very recent meta-analysis (Bhatia et al., 1998) shows the consistency of elevated risks in the epidemiology database and lends clear support to a causal association between increased risks for lung cancer and exposure to DE. Using 29 epidemiology studies, 23 of which met inclusion criteria, statistically significant relative risks (RR) for all studies were 1.33 (95% CI = 1.24-1.44). A subanalysis of case-control studies showed a RR of 1.33 (95% CI = 1.18-1.51); for studies that specifically controlled for smoking, the results were nearly identical. These findings play an important role in analytically showing the trend of the evidence across much of the epidemiology database. The quantitative findings of aggregate relative risks may also be useful for dose-response analysis, if individual study RRs are not thought to be suitable for some reason.

The relative risks from all studies with elevated risks, statistically significant or not, are on the low side, generally < 2. Several of the best individual studies have RRs in the 1.4-1.7 range. Low relative risks are harder to interpret as being definitive because of the possibility that unresolvable uncertainties could be responsible for or could be influencing the elevated risks. When only one or two positive studies with low RRs exist, there is some uncertainty about whether the inference of an effect is the proper interpretation, compared to a case in which several studies have low RRs, where the uncertainty is less and the inference that a real effect is being seen is more confident. With several low-RR diesel studies available and the meta-analysis clearly demonstrating the increased RR pattern, the low-RR situation would not discount the inference about an effect from exposure.

In most risk assessment situations positive epidemiologic findings are weighed within a framework of "causality" criteria. The causality framework, with its related biological factors and physical factors, helps to rationalize the increased epidemiologic responses within a broader context of plausibility. When these criteria are applied to the positive DE studies, all of them apply well. Other assessors using similar criteria may come to a different conclusion because there is no rigid attainment measure within the causality criteria.

With all evidence and analysis taken into account, it is concluded that the human evidence is "highly suggestive" of an association between DE exposure and lung cancer in retrospective occupational settings. This is just short of a more definitive finding of a "known" human carcinogen, primarily because of deficiencies in exposure information.

Human study evidence for other forms of cancer is inconclusive.

12.2.3.2. *Animal Evidence*

Animal studies show that DE is carcinogenic in test animals, which in the simplest sense raises a concern that DE has a carcinogenic potential in humans. The direct inhalation exposure rat studies are best for direct observation of inhalation responses. Chronic-exposure animal studies conducted prior to the 1980s did not use inhalation as the route of exposure; instead, exposure was artificially produced by lung implantation, intratracheal installation, subcutaneous and intraperitoneal injection, or dermal application. Of note here is that organic extracts from the particles, as well as the whole particles (with the absorbed organics), are carcinogenic in many of the older artificial exposure route assays.

When focused on the newer inhalation studies and recognizing the reproducibility of results, one concludes that if exposures are adequate, inhalation of diesel exhaust will induce lung cancer in rats and, under some conditions, in mice, albeit at higher concentrations than in rats. Generally, rats showed significant increases in lung tumors beginning at exposures of 2,200 $\mu g/m^3$ or higher (the human equivalent concentration [HEC] for 2,200 $\mu g/m^3$ is about 700-900 $\mu g/m^3$). These exposures are higher than those thought to be present in the human occupational studies (i.e., 125 up to 500 $\mu g/m^3$), which in turn are higher than the ambient exposures of interest for humans (e.g., 0.6-3.6 $\mu g/m^3$). Along with the increased tumor incidence in the rat studies, there was evidence of particle-induced inflammation and particle clearance overload in the lung. Exposures to rats below 2,200 µg/m^3 did not elicit an observable lung cancer response, while the accompanying evidence of inflammation trailed off more gradually as dose was lowered below 2,200; some inflammation was still seen at 1,000 µg/m^3. Inhalation of diesel exhaust has also induced significant increases in lung tumors in a few, but not all, strains of female mice; exposure concentrations of 6,000 µg/m^3 or greater were needed to see a significant response. Although responses were not detected in rats or mice at lower exposure concentrations of 350-2,200 µg/m^3, these studies with nominally 50 animals probably lack the sensitivity to reveal a threshold or a response to a less potent mode-of-action-driven carcinogenic process. Attempts to produce positive responses by inhalation exposure in Syrian golden hamsters, cats, or monkeys were unsuccessful. The negative results in cats and monkeys may be explained by an inadequate exposure duration (only 2 years) in these longer-lived species, whereas hamsters are known to be less sensitive to lung tumor induction compared to rats and mice.

There is convincing evidence, based on numerous published studies, that DE constituents are also mutagenic or, in a broader sense, genotoxic and/or carcinogenic. This supports the concern for a carcinogenic hazard for humans as well as suggesting possible mode-of-action and related approaches for low-dose risk estimation. The whole particle, particle extracts, and gaseous portions of diesel exhaust have been shown to cause changes in genetic material, which is not surprising because each component contains one or more mutagenic constituents. Human studies show increased formation of DNA adducts with DE exposure, and cultured human cells show an increased occurrence of sister chromatid exchange. Extensive studies with *Salmonella* have unequivocally demonstrated mutagenic activity in both particulate and gaseous fractions of DE. The induction of gene mutations has been reported in several in vitro mammalian cell lines after exposure to extracts of diesel particles. Particles have also induced structural chromosome aberrations and sister chromatid exchanges in mammalian cells. The question of germ-cell interaction, however, and the potential for human germ-cell mutagenic risk from exposure to diesel emissions remain unanswered.

12.2.4. Weight-of-Evidence Summary

A conclusion about the likelihood of a human carcinogenic hazard involves a weighing of the evidence from the human and animal studies, mode-of-action information, and evidence from ancillary studies. Scientific uncertainty or debates about some aspects of the evidence as well as different guidance about how to weigh evidence can easily lead to modestly different conclusions. EPA uses Carcinogen Risk Assessment Guidelines to frame its approach to weighing evidence and judging the likelihood of hazard. Overall, EPA considers that the human evidence for DE gives a clear signal about the likely presence of a human hazard. Subtle deficiencies in the human data influenced EPA in holding back a definitive call for a "known" human carcinogen based on the human data alone. Other conclusions that give a high likelihood to DE being a human carcinogen are also defensible. Animal evidence clearly shows that at high experimental exposures, DE produces lung cancer. Numerous DE particle extracts have been shown to pose carcinogenic hazards to animals and thus probably humans, even though some artificial exposure routes are used and carcinogenic responses are not necessarily in the lung. When mode-of-action information is considered, valid questions are raised about whether the lifetime rat bioassay, per se, is a good model for defining the hazard for humans at low exposures. Still, many of the individual components of the DE mixture are known or thought by the health science community to potentially pose a carcinogenic hazard. Supporting evidence for mutagenicity-genotoxicity in human cell cultures and in various other in vitro test systems for the whole DE mixture, the particle coatings, and the DE gases also support a likely mammalian-based carcinogenic hazard potential. For low levels of exposure, the hazard is hypothesized to be related to the organics present, while at high doses the presence of particles seems to exert a definite influence. Everything considered, EPA believes that DE is "very or highly likely" to be carcinogenic in humans by the inhalation route. This discussion and finding is consistent with the provisions of EPA's Proposed Cancer Risk Assessment Guidelines (U.S. EPA, 1996).

DE is considered to be a "probable" human carcinogen by inhalation exposure and to best fit into cancer weight-of-evidence category B1 according to EPA's 1986 Cancer Risk Assessment Guidelines (U.S. EPA, 1986). This conclusion evolves from positive yet "limited" evidence in the human studies, a "sufficient" level of evidence in bioassays, and consideration of the supporting information from mutagenicity and genotoxicity data.

In comparison with other agents classified into this category, the confidence in the DE weight-of-evidence call, on a relative scale of high, medium, or low, is on the high side. The conclusion that DE is a "probable" or a "very likely" rather than a "known" human carcinogen is due to several subtle limitations of the human studies, including the difficulty of reconstructing reliable estimates of exposures many years in the past, the lack of systematic quantitative records of ambient air quality, and the inability to completely eliminate confounding factors such as exposure to other pollutants, especially tobacco smoke, and the small increases in relative risk that make possible confounding more critical. The weight of the evidence for a human health hazard is nevertheless only just shy of being sufficient to view DE as a "known" human hazard, and for this reason "very likely" may be a better descriptor than "probable."

Once the hazard potential for humans is identified, information about the possible impact of the hazard (i.e., measures of risk and risk estimation, etc.) is treated as a related but separate dose-response issue. A complete conclusion about carcinogenicity thus has two components.

12.3. DOSE-RESPONSE ASSESSMENT

Dose-response assessment focuses on the relationship of exposure/dose to a biological response and how the response might change with dose; it also investigates the translation of this relationship to human low-exposure circumstances. The response(s) are the ones previously identified as important in the hazard assessment, and the low-dose aspects are approached by extrapolation, if appropriate, from an observable response range to lower exposure/dose levels, such as ambient levels of interest. Key dose-response assessment choices are influenced by definitive knowledge and informed reasoning about the mode of action. In the absence of such information, assumptions (i.e., defaults) are used, some of which may be conservative. Chapter 11 contains a more detailed review of dose-response issues.

12.3.1. Considerations in Modeling the Dose-Response Relationship

In order to know the extent to which a substance poses a hazard to human health, it is necessary to estimate the magnitude or incidence of adverse effects induced in humans by a particular concentration or dose of a substance. Since intentional experimentation with suspected toxicants on humans is not acceptable, animal studies are usually a major source of information about possible human hazards, yet the animals may have a variety of differences from humans that could affect the translation and extrapolation of the response. Animal studies usually involve exposure to high concentrations of toxicants, so that dose-response for low exposures must be inferred via informed assumptions and extrapolation. Even studies of humans are often at higher exposures than most individuals would experience at ambient conditions, so that conclusions about the effects of lower levels of exposure once again require assumptions and extrapolation.

Dose-response analysis of the positive human data may be approached in any of several ways, depending on what the data allow. One almost always has to struggle with exposure uncertainties when using retrospective human studies, as well as with questions of confounding exposure from other carcinogens, such as from smoking, when lung cancer is involved. Statistically significant mortality increases for lung cancer, in this case in cohort or case-control studies, may be useful analytical starting points. Adjustments in exposure dosimetry for humans wouldn't be needed, as is the case with animal studies.

In the DE dose-response analysis based on animal studies, several issues about exposure-dose to the lung can be reasonably accounted for because of available dosimetry research and modeling. The issues include species differences in particle deposition efficiency, particle clearance rates, lung surface area, respiratory rates, and transport of particles to lung-associated lymph nodes. Another set of issues involves the suitability of the rat model for assessing human risk from the standpoint of biological sensitivity as well as exposure-related MOA even after dose adjustment to equivalent concentrations. A final series of issues involves the choice of dose-response extrapolation model to be used (i.e., threshold or nonthreshold, linear or nonlinear, and biologically based or curve-fitting models).

While whole DE has multiple components, the various gaseous/semivolatile components of DE are in rough proportion to the particle concentration. Particle concentrations have been adopted by researchers to document whole DE mixture exposure and hence are used in this assessment as a dosimeter in evaluating carcinogenic and other adverse effects. For DE, the critical site of action is in the lower respiratory tract, particularly the alveolar region of the lung. The exposure route of concern for humans is inhalation, which is also the method of exposure used in some of the available experimental data, though important information from animal or other in vitro assays is gleaned from studies where the exposure is not related to inhalation per se but to artificial experimental exposures.

12.3.2. Dose-Response Assessment for Health Effects Other Than Cancer

A considerable body of evidence clearly shows a major noncancerous health hazard may be presented to the respiratory system following inhalation of DE. Based on pulmonary function and histopathological and histochemical effects, a rough estimate can be made concerning what chronic dose/exposure rates of DE (measured in terms of the concentration of diesel particulate matter) can be observed to cause an adverse effect and which exposures do not; this then is a starting point for establishing adequate margins of safety. A reliable experimental database and established EPA dose-response evaluation methods have been used to derive an inhalation reference concentration (RfC) for chronic exposure to DE as a guide in determining a level of long-term exposure that is thought to have an acceptable margin of safety from hazard for chronic exposure adverse effects other than cancer.

12.3.2.1. *Derivation of an Inhalation Reference Concentration*

The derivation of an inhalation reference concentration (RfC) for DE is a dose-response approach used by EPA for noncarcinogenic, threshold chronic effects. An RfC is defined as an estimate of a continuous inhalation exposure to the human population, including sensitive subgroups, with uncertainty spanning perhaps an order of magnitude, that is likely to be without appreciable risks of deleterious noncancer effects during a lifetime. The RfC approach is based on the assumption that a threshold exists for the human population below which no effect will occur.

As an alternative to using a no-observed-adverse-effect-level (NOAEL) in the RfC methodology as a dose-response marker, this assessment examined a benchmark dose/concentration (BMC) analysis approach, a newer approach that EPA has used to derive the RfCs for carbon disulfide, chlorodifluoromethane, and several other chemicals (U.S. EPA, 1995). The BMC refines the ascertainment of the NOAEL.

The database EPA chose to work from for RfC derivation consisted of 10 long-term (greater than 1 year) studies of inhalation of diesel engine emissions in laboratory rats. The available human studies, as discussed earlier, were qualitatively suggestive of adverse effects but were inadequate for RfC consideration. The selected rat studies were conducted by the Inhalation Toxicology Research Institute (ITRI) and the Japanese Health Effects Research Program (HERP). These studies were selected because each identified respiratory effects after chronic exposure and provided good information about pulmonary histopathology. Further, the selected studies spanned a wide range of exposures, from 350 to 7,000 $\mu g/m^3$ with three exposures in the 350-960 $\mu g/m^3$ range. Human equivalent concentrations were calculated using a dosimetry model developed by Yu et al. (1991) that accounted for species differences in respiratory exchange rates, particle deposition efficiency, differences in particle clearance rates at high and low doses, and transport of particles to lymph nodes.

The adopted RfC comes from the HERP study, which showed a NOAEL of 460 $\mu g/m^3$ (human equivalent concentration, HEC, = 155 $\mu g/m^3$). While particle overload is thought to be still present at 1,000 $\mu g/m^3$ to some degree, at 460 $\mu g/m^3$ the overload is thought to be much less, if not minimal. Consistent with standard RfC practice for a good chronic animal study, two types of uncertainty factors were used to further lower the NOAEL-HEC to a value having a sufficient margin of safety for humans. An uncertainty factor of 3 out of 10 was used to account for interspecies sensitivity; that is, humans could be somewhat more sensitive than rats. Out of a possible factor of 10, credit is given to the dosimetry adjustment procedures used. We would also note that some researchers believe rats could be more biologically sensitive than humans to DE particles, but we do not know whether rats are more or less sensitive to the organics. A second uncertainty factor of 10 is used to account for sensitive members within the human population, this being standard practice unless mechanistic or other data suggest otherwise. The resulting total uncertainty factor is 30. With 155 $\mu g/m^3$ divided by 30, the resulting RfC is:

RfC = 5 $\mu g/m^3$ of diesel particulate matter (DPM).

A BMC analysis also supports the use of an RfC of 5 micrograms per cubic meter of air. The derived RfC is considered reliable because of the high quality of the animal studies. Additional support for this RfC level is provided by a retrospective analysis of an earlier monkey study in which monkeys were exposed to DE at a concentration of 2,000 $\mu g/m^3$ for 2 years. Two years would be considered subchronic in this longer lived species. On the basis of minimal effects on the lungs of the monkeys, it could be argued that the exposure level is either a NOAEL or a marginal LOAEL (lowest observed adverse effect level). After adjustment to the equivalent human concentration and using appropriate uncertainty factors, an RfC value similar to that derived from the rat can be shown.

It is interesting to note that EPA's recently adopted particulate matter ($PM_{2.5}$) standard, with an adequate margin of safety, is 15 µg/m^3, as a 3-year average, based on human studies. The noncancer effects from DE are qualitatively similar to some of those for $PM_{2.5}$, though particle differences exist, as do the presence of absorbed organics and gases. A comparative discussion of the $PM_{2.5}$ standard and the DE RfC is not currently pursued in this assessment.

12.3.3. Dose-Response Assessment for Carcinogenic Effects

Evidence shows that DE is likely to induce lung cancer by the inhalation route of exposure, though the mode of action is imperfectly understood. Using a range of studies, some assumptions, extrapolation models, and animal-human dosimetry factors appropriate for DE, it is conceptually possible to estimate human cancer potency as a function of lifetime exposure assuming that DE is a human carcinogen.

12.3.3.1. *High- to Low-Dose Extrapolation and Mode-of-Action Considerations*

Because the biological mechanisms that result in cancer may be different for DE at low and high doses, a good understanding of the MOA would be needed in order to generate DE-specific, biologically based probability models for extrapolating from high to low doses. Currently, however, there are significant gaps in understanding of the mode of action(s) by which DE produces cancer, and thus the development of a rigorous DE-specific model is not pursuable. Given this imperfect situation, the risk assessor falls back on making choices about modeling, some of which can be informed choices while others are more public-health-driven policy choices.

To recount the mode of action discussion earlier, at low to high doses the DE cancer hazard is believed to have at least two modes. One involves mutagenic/genotoxic mechanisms associated with the organic substances adsorbed to DE particles as well as those in the gases. The organics include substances that are known to be mutagenic and/or carcinogenic in animal bioassays. Superoxide or hydroxal free radicals on the surface of fresh DE particles may also contribute to this mode of action. The mutagenic organics are present in approximate proportion to the particulate concentration, which likely varies somewhat by diesel engine circumstances. These substances could initiate cells or be complete carcinogens. A second mode involves nongenotoxic particle-specific mechanisms associated with lung particle overload, which is likely to dominate at high doses, according to rat studies, by exacerbating the promotion of initiated cells. The influence of the particles at low, nonoverload exposures may be limited to delivering organics, but this is an unknown.

If we favor the organics (gases or absorbed organics on the particles) as a likely etiologic agent for a suspected low-exposure carcinogenic hazard, the issue of bioavailability of the organics is an important consideration. There would be little doubt about the bioavailability of the gaseous-phase compounds in the DE mixture; whether they present a large enough dose to make a carcinogenic response observable is a different question. The bioavailability of the organics coating the particles is a more complex topic. Rat studies using radiolabeled BaP and nitropyrene-coated carbon particles have shown that lung retention time of the organic is significantly increased compared to a nonparticle instillation and that the gradual elution of BaP, for example, was faster than the lung clearance of the carrier particle itself. An understanding of the role extracellular fluids play in extracting the organics from the particles is unclear. Extraction of the organics by alveolar and other cell types is theorized but not well understood. At least in the rat and mouse models, a carcinogenic response was not seen below the whole-DE exposure levels that were also associated with particle overload, implying that a dose adequate to cause tumors was not present. On the other hand, one recent bioassay (Dasenbrock, 1996) has shown by intratracheal instillation that rat tumor yield is decreased (from 17% to 4%) when diesel particulates are stripped of their organics. Overall, limited data make it plausible to assume that there is a gradual release of organics from the particles, with resulting exposure to the respiratory epithelium.

Ideally, the dose-response curve that would be used to extrapolate from high to low exposures would reflect changes in the MOAs, a result of the possible transition from primarily nongenotoxic modes of action at high exposures to primarily genotoxic ones at lower exposures. However, data needed to construct this unifying dose-response curve are lacking. While the exposure levels at which primarily nongenotoxic MOAs may predominate can be inferred from lung pathology in rats (e.g., Chen and Oberdoster [1996] say the transition range probably lies in the >100 to 1,000 $\mu g/m^3$ exposure range for rats), the change in slope of the dose-response relationship can only be crudely approximated by the use of a biologically based model, some of whose parameters are estimated, or by estimating low dose risk from nonsignificant responses. In general, experimental studies inherently lack sensitivity for estimating dose-response in the low-dose range, except for extremely potent carcinogens, and DE seems not to be that potent. Use of human data to estimate low dose risks is also pursued, but this is not as robust as one would like because of the underlying exposure uncertainties and low relative risks limit, which for some assessors limits the confidence in the human-study-based risk estimates.

High- to low-dose extrapolations from various types of animal studies have been pursued using a variety of modeling concepts, all of which have low-dose linearity because of the inference of mutagenicity/genotoxicity. A variety of approaches is useful when information is inadequate to make a clear or reasonable call about the mode of action or when definitive insight into dose-response aspects is lacking. The margin of exposure (MOE) is also investigated for additional insight about the magnitude of extrapolation.

12.3.3.2. *Estimating the Cancer Risk of Diesel Exhaust*

In attempting to determine the cancer risk (i.e., potency) of DE, several kinds of studies and dose-response approaches were considered, including relative risks from epidemiologic studies, animal bioassay responses, a comparative potency approach, and the use of a biomarker, B[a]P, as a dosimeter.

12.3.3.2.1. ***Assessing risk using epidemiologic studies.*** As an ideal, epidemiology data are preferred for risk estimation if the available data are rigorous enough. One quantitative approach is to identify and use the dose-response relationship from an epidemiology study. This has been a debatable issue with the best of the epidemiologic studies, the cohort study of railroad workers by Garshick et al. (1988). This was a well-designed study with one of the largest cohorts. Because of the ongoing debate regarding the dose-response, EPA sees no benefit to generating more analysis of the issue until the cohort study can be updated or consensus can be reached about how to best use the current railroad worker cohort data. Garshick et al. (1987) also published a nested case-control study of the railroad workers, which showed increased relative risks of lung cancer from DE exposure. These can be used to back into a risk derivation by using a proportional population risk approach and overlaying this with separate assumptions about average exposure. For convenience EPA has started with a published proportional population risk analysis (McCellan, 1989) based on the Garshick case-control study relative risks. Additionally, EPA selected a reasonable exposure estimate of 125 $\mu g/m^3$ (and also included 500 $\mu g/m^3$ for comparison), corrected the numerical risk estimates for occupational versus ambient exposure, and thus back-calculated equivalent estimates of unit cancer risk. The resulting risk estimates have 95% upper and lower bounds as well as MLE values.

The adoption of a particular exposure value for risk derivation from the railroad worker study is a critical choice since risk magnitude is directly proportional to the exposure. The true exposure of the railroad workers beginning in the late 1940s–1980s period is an unknown, though Woskie (1988a, b) in conjunction with the railroad worker epidemiology study, evaluated current levels of exposure for the railroad worker job categories. Woskie sought to evaluate the current exposures and comment on historical exposures for railroad workers by job category and did so by collecting limited personal monitoring data for the job categories as well as employing modifying factors to account for a number of influencing factors. The job category exposure estimates for the late 1980s showed that geometric mean exposures might range across all job categories from about 17 μ/m^3 to 134 $\mu g/m^3$ at a 95% confidence level, these included an adjustment for cigarette smoke. It was also suggested that exposures were approximately constant over the 1950s to 1980s given the circumstances of railroads that were sampled in the study. National projections were slightly higher at 31–35 µg/m^3 up to 125–157 µg/m^3. Woskie mentions that anecdotal reports suggest that exposures were likely higher in the early period versus the later years due to, for example, minimal ventilation, but the magnitude of difference could be ascertained.

From these crude approximations, one has to make a choice as to how appropriate overall estimates of 125 or 500 µg/m^3 are. Woskie's work would suggest that 125 is a reasonable choice and that 500 seems too high. Woskie's estimates were for worker shifts, while EPA's interest would be for a 24-hour exposure which could be a lower value. The diesel locomotive engines went through two generations, the first generation lasting through the 1950s, with a second generation starting to appear in the 1960s. Woskie's data was mostly derived from first generation engines that were still in use in the 1980s and which probably were higher emitters of DPM. The selection of 500 µg/m^3 has no particular support, though it can't be ruled out. It does show the sensitivity of the risk calculations to a fourfold higher (125 vs 500) exposure estimate.

An exposure estimate of 125 µg/m^3 is in general agreement with measurements made during the period of the underlying railroad worker study. As there is indirect evidence, but few actual measurements, indicating that historical occupational exposures were higher, the use of 125 µg/m^3 is a reasonable conservative choice, though not without uncertainty. The selection of a best exposure value is an unresolvable question, though reason would suggest that the true exposures are in this range.

For each exposure, three estimates of risk can be provided: an upper end, an MLE (maximum likelihood estimate), and a lower end. The case- control, proportional risk study-based estimates define a range as follows:

Exposure = 125 µg/m^3:	Upper end risk	200×10^{-5} per µg/m^3
	MLE is	100×10^{-5}
	Lower end risk	10×10^{-5}
Exposure = 500 µg/m^3:	Upper end risk	50×10^{-5}
	MLE is	30×10^{-5}
	Lower end risk	3×10^{-5}

Upper bound from biomarker (BaP) ~ 1×10^{-5} per µg/m^3 (as discussed in next section, MLE = 0.26×10^{-5})

EPA is aware that the authors of the proportional risk analysis may have some reservations about their conclusions using the case-control study, given the dose-response debate about the larger cohort study, but EPA risk assessors believe the merit of using the case study relative risks is not diminished by the cohort study debate.

A few comments about the human databased estimates are important to the question: How good are they? The average occupational exposure of 125 µg/m^3 is unlikely to be large enough to induce lung particle overload in humans (a human level of 500 µg/m^3 is likely to be in the overload range, extrapolating from rat studies). When using an average estimate for exposure, we must remember that about half the time the exposures are higher, and while noting that occupational exposure occurs about 40 h per week, the long-term occupational exposure is less than lifetime, and thus mean particle concentrations adjusted to continuous exposure are unlikely to exceed 100 µg/m^3 and may be notably lower. Because cancer induction at nonparticle- overload conditions is reasoned to be influenced by the mutagenically active organic fraction and perhaps by the oxygen radicals present in fresh exhaust, the use of linearized low-dose extrapolation is a supportable modeling approach. Individual smoking data were obtained in the Garshick et al. (1987) case-control study, as was information about possible asbestos exposure, thus eliminating a major potential source of bias. Also, relative risk ratios from other diesel epidemiologic studies did not differ greatly from the 1.41 (CI = 1.06, 1.88) reported in the Garshick et al. (1987) study, increasing confidence in the Garshick-based relative risk findings. For example, in a recent meta-analysis of 34 studies by the State of California (Cal-EPA, 1997a) relative risk ratios ranging from 1.12 to 1.43 were derived, depending on the model used and whether or not they were corrected for smoking.

Exposure estimation is a notable uncertainty in the risk estimates derived from the railroad worker case control study. However, according to Woskie et al. (1988), the 125 µg/m^3 estimate was probably reasonable as an average exposure near the end of the study period. The EPA risk estimate of 200×10^{-5} per µg/m^3 defines the high end of a range of plausible upper-bound estimates for DE cancer risk, while 3×10^{-5} µg/m^3 defines the lowest end of the human data range. The MLEs of the two exposure scenarios define a tighter range of $30\text{-}100 \times 10^{-5}$ per µg/m^3.

12.3.3.2.2. ***Assessing risk using a biomarker.*** A second approach using human data is the use of a biomarker as a dosimeter. Pike and Henderson (1981) related the concentration of benzo[a]pyrene (B[a]P) to smokers, British gas workers, U.S. coke oven workers, U.S. hot pitch workers, and residents of rural and urban locations and found good agreement in predicting lung cancer risk. They concluded that while B[a]P is not the only carcinogen present in DE, and perhaps not even the most important, it is a reasonably accurate dosimeter for assessing risk from combustion or pyrolysis of petroleum products or tobacco and could therefore be appropriately used for DE risk assessment. Based on Pike and Henderson's estimated lung cancer risk of 1/1,500 per ng/m^3 B[a]P and a reported B[a]P concentration of 3.9 ng per µg of diesel particulate matter in exhaust from a Volkswagen engine (Heinrich et al., 1995), a maximum likelihood estimate of lung cancer risk of 2.6×10^{-6} per µg/m^3 of diesel particulate matter can be derived. The 95% upper bound of this value, while not calculated by the authors, is near 1×10^{-5} per µg/m^3.

A strength of the biomarker approach is its moderately good accuracy in estimating cancer risk from exposure to a number of combustion/pyrolysis pollutants using B[a]P as a dosimeter. However, while most of the combustion products assessed in the study contain organics similar to DE, unlike DE they have little or no insoluble particulate matter. Although this approach, like the comparative potency method, fails to account for the carcinogenic effect of the particle itself or for modifications in potency because of the association of the organic component with particles, the human exposures of interest presumably don't have particle-driven effects either. Of course, the B[a]P concentration might also vary in diesel samples because of different types and sizes of engines being run under varying conditions and using different fuels.

12.3.3.2.3. ***Assessing risk using animal studies.*** Previous EPA attempts to quantitatively estimate cancer risk based upon chronic rat bioassays used some form of a linearized model to extrapolate risk to low doses. This approach was based upon the assumption that cancer response is a direct function of exposure concentration at all exposure levels. As discussed previously, this assumption is no longer supported by the available data because of the apparent difference in mode of action at high versus low exposures. At high concentrations, rat lung cancer is believed to be induced by an interaction of particle overload with associated pathology, carcinogenic organics, and possibly oxygen free radicals. At lower doses, only the latter two are likely to have a major impact. This is likely to result in a dose-response curve that is nonlinear at least in the high-dose region. Unfortunately, the animal bioassays lack sensitivity, in particular, the number of animals per group are too small to directly measure low-dose responses or show clearly where the mode of action transition occurs on the dose-response curve. Clearly, at exposures above 2,200 µg/m^3 the dose response would be nonlinear. At some exposure level below 2,200, the particle driven mode of action is diminished. For environmental levels of exposure, the risk estimation objective would be to partition the dose-response curve and develop risk estimates from the low-exposure portion.

Several quantitative modeling approaches were used with animal data to gain some insight about low exposure only risks—none were completely satisfactory. The simplest approach is to derive a 95% upper-bound estimate of risk using the highest concentrations of DE not inducing pathologic responses and lung cancer. This conceptually places an upper bound on risk using elevated but not statistically significant responses. The low-dose groups from the Mauderly and Ishinishi studies (i.e., concentrations < 500 µg/m^3) are suitable for such an analysis. Combining these studies increases the statistical power somewhat, though the variability statistics of the minimal response would tend to increase the risk estimate. The resulting risk estimate using a linear multistage extrapolation model (LMS) is 19 x 10^{-5} per µg/m^3. This is several fold higher than LMS estimates using all (including the high-dose responses) exposure groups (about 3.4 x 10^{-5}) but approaches the higher risks suggested by the human data.

An alternative approach (mentioned in EPA's *Proposed Guidelines for Carcinogen Risk Assesment*) involves identifying a point of departure on the dose-response curve, perhaps ED_{10} or ED_{01}, the concentrations inducing carcinogenic responses in 10% or 1% of the animals, and then extrapolating risk from that point as long as extrapolation was justifiable. This was done for the rat data, both ED_{10} and ED_{01} risks were estimated using an LMS model. The answer was nearly identical to the 3.4 x 10^{-5} obtained from using the entire dose-response data. The linear model seems insensitive for this particular data set.

A third approach published by Chen and Oberdörster (1996) involved development of a biologically based dose-response (BBDR) extrapolation model. They applied it to the rat dose-response data to consider the risk sensitivity to a threshold-particle driven MOA compared with a nonthreshold-mutagen driven MOA. If particle effects are assumed at all concentrations, i.e., no threshold for particle effects, then the model predicts risk virtually identical to those predicted by the linearized multistage model. If a threshold for particle-induced cancer effects is assumed at 1,000 µg/m^3, the BBDR risk estimate is about fivefold lower at a concentration of 1 µg/m^3. This difference is consistent with the hypothesis that organics and oxygen radicals play a more important role as concentration becomes lower. The results, however, only suggest the influence of mutagenic-nonthreshold versus mutagenic-threshold modes of action, because data are insufficient to validate the model.

There is also some debate, and hence uncertainty, regarding the biological adequacy of the rat as a model for evaluating any human risk. This begs the question whether rats may be uniquely sensitive to particle-induced cancer, perhaps because of their different respiratory tract anatomy. Only two other rodent species have been adequately tested, hamsters and mice. The response in mice was equivocal, and negative in hamsters. Hamsters, which do not respond to DE exposure, are resistant to induction of lung cancer from DE. Since there is evidence for human carcinogenicity of DE in epidemiologic studies, one could argue that the rat may be more qualitatively similar to humans in response to this agent than are the other laboratory species. Furthermore, rats have been shown to respond similarly to humans when exposed to cigarette smoke (Finch et al., 1995). Although the rat could be more sensitive from a particle standpoint, we wouldn't necessarily say the same in regard to the organic components, which are playing a role as well. Thus, while the use of rat data does involve uncertainty, it is not justifiable to fully discount the rat as a plausible model for establishing a range of possible human risk from exposure to DE.

A strength of rat-based risk estimates is that the studies are of good quality and provide tumor responses that are in essential agreement with one another. Another strength is the ability to use a sophisticated dosimetry model to derive equivalent target tissue concentrations between rats and humans. However, with all statistically significant rat responses occurring at exposures where particle overload is also occurring, the use of rat data to define possible risk in any manner has distinct shortcomings and resulting uncertainties. For reference purposes, an LMS-derived averaged risk estimate of 3.4×10^{-5} per $\mu g/m^3$ was calculated from the high-dose rat responses of Mauderly, Ishinishi, and Brightwell. Use of measured rather than modeled lung particle burdens from the Mauderly et al. (1987) study did not significantly affect results. As a matter of curiosity, if dose equivalence is based on lung burden per unit body weight$^{3/4}$, a more traditional means of species extrapolation for organics, LMS risk estimates would increase about threefold.

As it turns out, all of the rat-based risk estimates are near the low end of estimated risks.

12.3.3.2.4. ***Assessing risk using a comparative potency method*****.** A third approach, developed before either animal bioassay or human epidemiologic data became available, is the comparative potency method of Albert et al. (1983). In this method, exhaust particle extracts obtained from three light-duty engines, manufactured by Nissan, General Motors, and Volkswagen, and a Caterpillar heavy-duty engine were evaluated for potency in a variety of short-term tests. The ratios of potencies of these extracts were then multiplied by the unit risk estimates of related combustion or pyrolysis products, such as roofing tar, cigarette smoke condensate, and coke oven emissions, for which unit risk estimates based on human data had already been derived. The potency ratio of DE to each of these was multiplied by their unit risk estimate. Using this method Albert et al. (1983) derived a unit risk estimate for DE averaging about 3×10^{-5} per $\mu g/m^3$.

The comparative potency method was developed more than 15 years ago because bioassay data were lacking at the time and because it was believed that cancer induction was a function of the organic components. Conceptually, this approach can still be of use in rationalizing lower limits on risk. However, one must accept the assumption that relative potency in short-term tests will be similar to relative potency for lung cancer induction. Any reluctance may be balanced by considerable reliance on dermal exposure in some of the short-term studies. Since both skin and lungs are epithelial tissues, confidence that relative potencies are similar increases. Another possible weakness in the comparative approach is a failure to account for potential differences in the relative bioavailability of the organic fraction during exposure to whole exhaust versus exposure to particle extracts, or the possibility that association of organics with particles may alter their effectiveness. It is not known whether these issues raise significant concerns.

Tabular summary of animal-based risk estimates

19×10^{-5} per µg/m^3	Upper limit from low-dose rat studies
3.4×10^{-5} per µg/m^3	Upper bound from high-dose rat responses
3×10^{-5} per µg/m^3	Upper bound from BaP comparative potency analysis
1×10^{-5} per µg/m^3	Linear extrapolation using BBDR model

12.3.3.3. *Bounds for Cancer Risk and Margin of Exposure*

Each of the dose-response and risk derivation approaches, using human or animal data, has known uncertainties that seemingly preclude selecting one as the "most scientifically valid" or best estimate. Taken collectively, the approaches provide a numerical basis for defining a range of plausible upper-bound risks, upper-bound meaning that conservative assumptions (e.g., linear low-dose extrapolation) have been used and this is not likely to result in an underestimate of risk.

For the reasons cited earlier, the risk estimate of 2×10^{-3} per µg/m^3 from human studies is the highest estimate and thus defines the upper-end value for a range of estimates. Three different animal-based approaches that assumed that lung cancer at low doses is a function of the organic components (the comparative potency method, the biomarker method, and low-dose estimation of risk from nonsignificant rat response data) resulted in upper-bound risk estimates from near 1×10^{-5} up to 19×10^{-5} per µg/m^3. A BaP human biomarker-based estimate of 0.26×10^{-5} as an MLE also exists, with an upper bound of the MLE being about 1×10^{-5}. Since no threshold is assumed for the organic components of DE, if particles do contribute to risk at low exposures, the upper bound may not be as conservative as would normally be the case, i.e., normally we would say the true risk, which is not definable, could be between the upper bound and be as low as zero. The 1×10^{-5} per µg/m^3 risk estimate from various animal-based approaches seems to be a floor of all estimates and therefore, establishes the low end for a range of risks.

The upper-end risk estimate of 2×10^{-3} per µg/m^3 from the epidemiologic study is based on an assumed long-term average exposure of 125 µg/m^3. If a higher exposure were chosen the risk estimate would decrease by a proportional amount. Risk estimates based upon animal bioassays, comparative potency, and the biomarker approach are as much as 200 times lower. The range of possible human risks encompasses mixed MOA assumptions and does not fully discount any experimental animal model system. Given the presence of known uncertainties with the adequacy of the various animal test systems as a predictor of human hazard, and with the uncertainties for the railroad worker exposures, neither the human nor animal test system provides a scientifically compelling basis for selection of a single best risk estimate. Therefore, a range of plausible risk estimates is recommended to characterize the possible public health impact of exposure. Public health policy preferences might be appropriate, such as recognizing that the human data-based estimates at least avoid uncertainties of species extrapolation and biological relevance associated with the animal estimates, and thus a preference for the range of human data- based risk estimates would be reasonable. An argument also could be made that the human estimates derived from 125 $\mu g/m^3$ exposure have more support than 500 $\mu g/m^3$ because Woskie's assessment was more consistent with a level of 125. Some may also favor the MLE risk estimates from exposure assumptions of 125 and 500 as a preferable selection of risks.

Upper bound risks ranging from 1×10^{-5} to 200×10^{-5} (i.e., 2×10^{-3}) per $\mu g/m^3$ are recommended for bounding the risk of human lung cancer induced by exposure to DE. The risk estimates evolving directly from human data run from 3 to 200×10^{-5} per $\mu g/m^3$, with a subrange of maximum likelihood estimates spanning $30\text{-}100 \times 10^{-5}$ per $\mu g/m^3$. Animal-based estimates range from 1 to 19×10^{-5} per $\mu g/m^3$.

It may be insightful to consider the margin of exposure (MOE) for these risk estimates. An MOE compares ambient exposure of interest to LOAELs (adjusted to human equivalent LOAELs) from the human and from the animal studies. The resulting margin shows the extrapolation range from, e.g., an observable cancerous effect level to an ambient human exposure of interest. The margin value illustratates the range of extrapolation that has occurred when risk models have been employed to predict dose-response below the observable data. The greater the magnitude of extrapolation, i.e., the margin, the more general uncertainty there is. If 2 $\mu g/m^3$ is an ambient human DE exposure of interest, if an estimate of 125 $\mu g/m^3$ is selected from many possible choices for the human study of railroad workers, and 3.5 mg/m^3 is a LOAEL rat exposure from the Mauderly rat study (human equivalent concentration: 0.36 mg/m^3 = 360 $\mu g/m^3$ after adjusting to continuous exposure conditions and across species), all of the human equivalent exposure information needed for an MOE comparison is available. What is seen is that the range of extrapolation from the human studies is about 1/3 of that for the animal studies, thus suggesting a reduced margin for uncertainty compared to animal estimates. The ambient levels of interest are nevertheless 10-60 times lower than the lower of the exposure scenarios associated with the human studies.

The MOE comparison is displayed graphically in Figure 12-1. This figure may provide a clearer picture of the relationship between exposure and various risk estimation recommendations coming from this assessment.

12.3.4. Susceptible Subgroups

The hazards previously identified, i.e., acute symptoms including exacerbation of asthma, and chronic effects such as reduced pulmonary functions and other respiratory weaknesses, are assumed to be possible consequences in individuals of average health and in their adult years. Individuals with preexisting lung burdens of particulates may have may have less of a margin of safety from DE hazard consequences, though this cannot be quantified. In reality, DE exposure is probably additive to many other minute or larger exposures to mutagenic organics and particulate matter, but the magnitude of this additivity has not been estimated in this assessment. For example, adults who predispose their lungs to increased particle retention (e.g., smoking or high particulate burdens from nondiesel sources), have existing respiratory or lung inflammation or repeated respiratory infections, or have chronic bronchitis, asthma, or fibrosis (e.g., silica exposure) would have a much lower margin of safety and thus would be at greater hazard from DE exposure. It hasn't been shown per se in DE studies, but infants and children may have a greater susceptibility to the acute/chronic toxicity of DE for the conventional public health reason

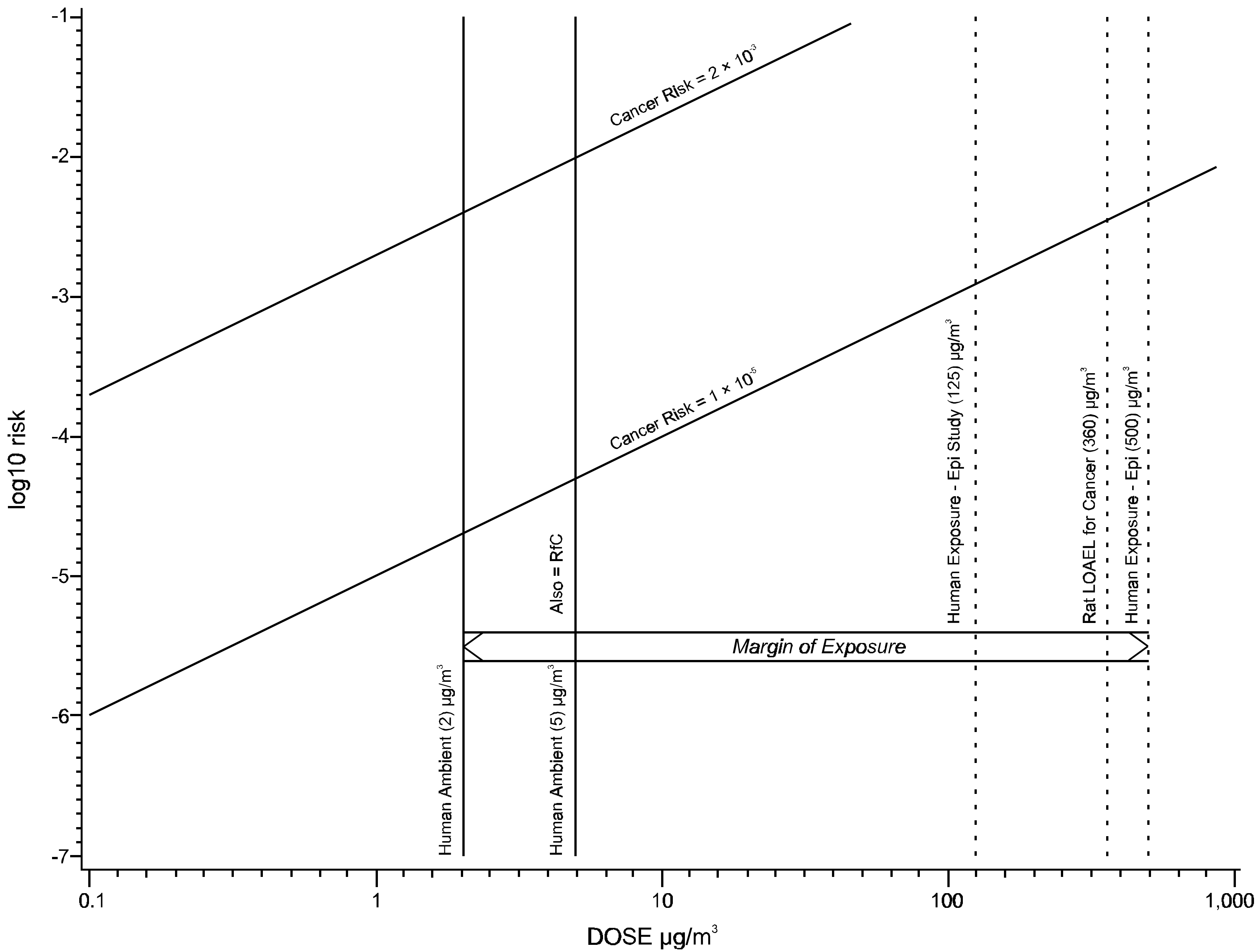

Figure 12-1. Comparison of cancer risks, RfC, and MOE.

that their developing pulmonary and immunologic systems may be more susceptible than an average adult's.

12.3.5. Other Comprehensive Diesel Exhaust Health Assessments in the United States

In 1997 Cal-EPA (California Environmental Protection Agency) released a draft hazard and risk assessment for DE emissions. Cal-EPA concluded that a reasonable, very likely explanation for the increased risks of lung cancer seen in experimental animal and epidemiologic studies is a bona fide causal association between DE exposure and lung cancer. Because of evidence for both carcinogenic and noncarcinogenic toxic effects, they also proposed to list DE as a toxic air contaminant in California. Their conclusion for the carcinogenic hazard is similar but not identical to EPA's, (i.e., DE is highly likely to be carcinogenic in humans). Cal-EPA also provided a range for cancer risk per unit of lifetime exposure that is virtually identical to EPA's risk range. The Cal-EPA risk range included a subrange of estimates from the animal studies and a subrange of estimates from the human studies, as has EPA in this assessment. EPA indicates that DE is "highly likely" to be a human carcinogen, whereas Cal-EPA is slightly more certain about the likelihood. Given the health data uncertainties, data gaps, and the discretionary choices that are made in risk assessment, the differences in the EPA and Cal-EPA assessment findings are not significant. Cal-EPA's recommendations for noncancer respiratory hazards are identical to EPA's because they adopted the EPA RfC of 5 $\mu g/m^3$. As of February 1998, the Cal-EPA assessment was still in draft.

12.4. EXPOSURE PERSPECTIVE

Diesel emissions are complex mixtures containing thousands of organic and inorganic constituents in both gas and particulate phases with differing chemical reactivities. After entering the atmosphere, they are transported and transformed according to their distinctive characteristics, undergoing physical and chemical changes that may form secondary pollutants more harmful than their predecessors. Thus, a knowledge of diesel emissions at or near their sources is not sufficient to fully assess their impact on human health and welfare. However, data on how DE contributes to exposure levels for these secondary pollutants are currently lacking.

Determining the amount of DE present in the ambient air is also complicated by the difficulty of distinguishing organic compounds and particles that originate in diesel engines from those that originate in gasoline engines or come from other sources. This source speciation is not well sorted out in the ambient characterization of DE.

Nonoccupational exposure to DE is worldwide in urban areas, with lesser exposure in rural areas. Certain working populations are also exposed to higher levels of DE than the rest of the population. The level of exposure will differ within geographic areas based on the number and types of diesel engines in the area, as well as atmospheric patterns of dispersal and the location of the individual relative to the emission sources.

While a detailed exposure assessment for DE has not been conducted as part of this study, the following exposure data are provided to give some context for the hazard assessment and dose-response analysis.

Estimates of annual average concentrations of particulate matter in the ambient air, published in Chapter 9 of EPA's Motor Vehicle-Related Air Toxics Study (U.S. EPA, 1993), may be used to generate a crude estimate of the concentration of particulates from diesel exhaust in the ambient air. The total concentration of particulates from DE in ambient air in urban areas for 1995 was estimated as 2 $\mu g/m^3$, the concentration in rural areas as 0.6 $\mu g/m^3$, and the nationwide average concentration as 1.1 $\mu g/m^3$.

In an alternative estimation, using ambient monitoring data, total suspended particulate matter (TSP) for 1990 was determined to equal 48 $\mu g/m^3$. With approximately 5% of total particulate matter associated with DE, multiplication of the total by the fraction contributed by diesel exhaust and adjusting for time spent indoors results in an integrated estimate of 1.5 $\mu g/m^3$, according to EPA's hazardous air pollution exposure model (HAP-EM, 1988).

Exposure estimates for more highly polluted locations are somewhat greater. Estimated mean concentrations of DPM for Los Angeles were reported to be 2.7 $\mu g/m^3$ (Sienicki and Mago, 1992). McClellan (1986) estimated concentrations on urban freeways and street canyons to be as great as 15 $\mu g/m^3$.

Recent Cal-EPA (1996) studies show winter period estimates in three California locations for diesel PM_{10} of 4 to 22 $\mu g/m^3$. A broader Cal-EPA analysis shows average ambient outdoor diesel PM_{10} to range from 0.2 to 3.6 $\mu g/m^3$ across 14 California air basins with a population-weighted average of 3.2 $\mu g/m^3$. Concentrations in occupational settings may be higher.

Recent studies, including a study of the Baltimore Harbor Tunnel (conducted by the Desert Research Laboratory for the American Petroleum Institute) and an ORD measurement study of tailpipe emissions from a moving heavy duty diesel truck, have confirmed that dioxins are formed and emitted from heavy-duty diesel trucks. ORD's draft dioxin source emission inventory, being developed as part of the ongoing Dioxin Reassessment effort and scheduled to undergo peer review in April 1998 estimates that 60 g TEQ are emitted from U.S. trucks. When this estimate is compared with total estimated U.S. emissions of 3,000 g TEQ, it appears that diesel trucks are not a major dioxin source. However, it is unknown whether such emissions could have significant local impacts, since current information does not permit us to rule out the possibility of exposures of interest. The types of exposures that have been of particular concern from stationary dioxin sources, e.g., incinerators, have been noninhalation exposures associated with ingestion of certain foods, e.g., beef and vegetables, contaminated by the deposition of stack-emitted dioxin. There is a potential for deposition of stack emissions from trucks to soil and water adjacent to some highways resulting in similar impacts. We recommend that appropriate data be collected.

The changing composition of DE (i.e., older engines vs. newer technology ones, heavy-duty vs. light-duty, and engines run under varied operating conditions) gives rise to questions about how the health data and the risk assessment findings in this report, which are based on pre-1998 engines, can be applied to present-day engine exhaust emissions and resulting ambient exposures. This is a complex question that is not rigorously addressed in this assessment. It is clear that newer technology engines will have somewhat different emission composition (i.e., perhaps reduced NO_x with increased fine particles), not to mention emission controls, which would reduce certain exhaust components, presumably larger particles. Since particle mass is the surrogate dosimeter used to correlate toxicity with exposure and public health impact, the implication is that we have a basis for scaling to account for exhaust changes. This relationship may be too simplistic, and thus further investigations of current-day emissions, and how they average out across the fleet or stationary engine use, may be warranted.

12.5. DIESEL EXHAUST HEALTH RISKS—A PLAIN-LANGUAGE OVERVIEW OF KEY INFORMATION

This section reviews key information about diesel emission hazards and risks by posing and answering simple questions. It is mostly duplicative of information found earlier in this chapter, though some added explanation has been added for background purposes.

What is diesel exhaust (DE)? What happens when it enters the environment?

Diesel engines are very durable and have performance characteristics that make them a desirable alternative in certain uses. The diesel engine, whether it be in an automobile, truck, off-road equipment, locomotive, or ship, produces exhaust from the combustion of diesel fuel. The exhaust is a mixture of organics and inorganic constituents (i.e., products of incomplete combustion). The exhaust can be invisible or be seen as a gray or black smoke. When visible, what is seen is the particle fraction of the exhaust mixture, usually from an engine that is not required to control its emission or one that is not well maintained. In the simplest terms, DE is a mixture of carbon core particles that have a coating of various inorganic/organic compounds, as well as gases and semivolatiles. The identifiable organic and inorganic compounds number in the hundreds. The particles have a spongelike structure and a very large surface area per gram, which make them an excellent carrier for adsorbed inorganic/organic compounds. The amount of specific chemical compounds present and the size of the particles depends on the engine design, load, operating speed, fuel consumption, and whether or not the engine is in a well-maintained state. The diameter of diesel particles is very small, typically 0.1 to 0.25 µm, with more than 75% of the particles smaller than 1 µm. Light-duty diesel engines emit 50-80 times and heavy-duty engines 100-200 times more particulate matter than catalytically equipped gasoline engines. The heavy-duty and off-road diesel engines, as a group, account for most of the DE particulate emissions discharged into ambient air.

When the exhaust first escapes to the ambient air it is called “fresh” exhaust, which also connotes some increased chemical and biological reactivity properties, compared to “aged” exhaust, which after a day or so has diminished reactivity. Once in the ambient air, some of the organic, inorganic compounds and oxygen free radicals associated with the fresh exhaust begin to transform into other chemical compounds because of their exposure to sunlight or other atmospheric elements. The exhaust mixture also becomes dispersed and thus diluted in the ambient air. The topography and/or climatic conditions in a particular area may promote dispersal, or in some cases hinder dispersal to the point of causing a slow accumulation of DE components, e.g., because of ground-level air stagnation. The particle fraction of DE contributes to the background ambient particulate matter (PM) in the air, while the various gaseous inorganic/organic components add to other background loadings in the ambient air.

The measurement of whole DE is complex because it is a mixture of particles and gases. The approach adopted by researchers has been to use particle mass as a surrogate for the whole mixture. The mass measurement is in units of weight (µg, microgram) per volume of air (m^3, cubic meter). This emphasizes the particle fraction of the whole DE mixture together with its adsorbed organic/inorganic components, rather than the gaseous organic/inorganic constituents. The latter are, however, in relative proportion to the particle mass present.

How are individuals exposed to DE? How does it enter and leave the human body? Is there a test to determine whether exposure has occurred?

Individuals may be exposed to DE when they are in an area where diesel engines are in use and the exhaust mixture is breathable. Diesel engines are nearly everywhere, so it becomes a matter of relative frequency of contact (i.e., exposure), duration of exposure, and concentration of the exhaust mixture. Some occupational settings may be prone to more frequent and higher exposures, such as in engine maintenance shops, heavy equipment operations, mining, or bus terminal operations, to suggest a few. A nonoccupational setting that may have a higher than average ambient exposure could be, for example, among those who spend a notable part of their day in the vicinity of diesel roadway traffic, such as in or around highways or urban street canyons. For some DE emissions, one can see smoke or soot, indicating that some relatively large particles are present. Emissions with the more typical small-diameter particle are virtually invisible. The odor threshold, at least according to one study, is about 200 µg/m^3 of particulate, or greater.

This assessment does not determine exposure levels across the population, but some exposure estimates from various sources are noted to provide a frame of reference. For example, several evaluations show average rural and urban ambient levels of DE to be in the range of 0.6-3.2 $\mu g/m^3$. Recent California-EPA studies show winter-period estimates in three California locations for diesel PM_{10} (particulate matter < 10 um) of 4 to 22 $\mu g/m^3$. A broader Cal-EPA analysis shows average ambient outdoor diesel PM_{10} to range from 0.2 to 3.6 $\mu g/m^3$ across 14 California air basins with a population-weighted average of 3.2 $\mu g/m^3$. Concentrations in occupational settings may be higher.

DE exhaust most easily enters the body by breathing, though in some occupations portions of the exhaust may cling to skin or hair and thereafter possibly be ingested as a consequence of hand-to-mouth activity. By far, the major exposure pathway is from breathing.

Once inhaled into the nasal passage, some DE mixture components could be deposited or absorbed along the upper nasal and respiratory tract, but most of the mixture travels into the lungs where the particles and gases are deposited on lung tissue. The inhale-exhale pattern of breathing results in some exhalation of the particles and gases; the remaining particles stay in the lung until the body's natural defense mechanisms mobilize to clear them out. The remaining gases and organics/inorganics coated on the particles are eventually absorbed into the lung tissue, then into the bloodstream, and thereafter begin a process of normal detoxification by various body organs followed by removal from the body via urine and feces.

There is no single medical test to determine if a DE exposure has occurred. Many symptoms of episodic DE exposure are similar to symptoms caused by other agents or, in some cases, the onset of a common cold. Invasive sampling of particle deposits in the upper respiratory tract or lung could be done, yet such particles may not be readily distinguishable from particulate matter from other sources.

How does exposure affect human health and how certain are we about these effects?

One way to consider the possible harmful effects of DE is to consider acute exposure (i.e., episodic/infrequent contact) versus chronic exposure (i.e., fairly continuous over long periods of time, such as years). As the exposure frequency and/or duration of the contact increase, acute exposure and its effects give way to chronic exposure and its consequences. Most health studies are designed to evaluate either acute or chronic effects. Another aspect of the exposure event is to realize that in a general sense *total cumulative exposure and the rate at which the exposure is received in some manner influences the nature and/or the extent of a harmful effect, this being a traditional toxicological concept not unique to DE*. This relationship is not always definable in a rigorous way, but is useful as a concept in relating exposure features to toxic consequences. Many DE components have a potential of being harmful because they are toxic at some exposure in their own right. A DE component may start out being toxic, may start out being nontoxic but be changed into a toxic substance by the body's defense mechanisms, or have no toxicity at all in any phase. The question is, do the concentrations in the DE mixture, when taken as a total, cause harmful effects?

The pure carbon core DE particle, the organics coating the particle, and the gas/vapor phase components of the mixture all have health study evidence that shows toxicity, and thus potential to be hazardous under some regime of exposure. Taken individually, both the particles and some of the chemical compounds can be irritants and cause inflammation in the respiratory system, or in larger amounts cause more permanent harmful effects. For example, among the many hydrocarbons found in DE, 19 of them are believed or known to pose a human carcinogenicity hazard, with the magnitude of the risk thought to be proportional to total exposure over a lifetime. It is not clear precisely what components of the DE mixture are key to causing the acute effects or the more permanent chronic effects and, in fact, most of the components may play a role, which may change as the human exposure changes from low to higher levels.

Effects of acute exposure on humans have not been systematically and comprehensively studied, but there are some symptoms seen, depending on the person and the concentration of DE. The symptoms are a biological response to irritation of human tissues. The symptoms range from no effect, to annoying and quickly passing effects, to effects that cause temporary impairment, up to and including symptoms that may indicate permanent impairment. e.g., from a very high one-time exposure. Examples at the lower levels include: headache, runny eyes and nose, or nausea, up to and including restricted breathing due to respiratory resistance (asthmalike response). Immunologic allergic reactions resulting in long-term hypersensitivity to DE and perhaps other ambient agents may also be possible, according to some very recent human and animal research. Animal studies have confirmed the irritational aspects of contact with DE and further suggest that high acute exposures may cause lung damage. The supposition is that different people have different levels of tolerance or susceptibility and that the higher the exposure, the more likely people are, in general, to experience an unpleasant symptom or perhaps have a more permanent adverse effect such as hypersensitivity or lung damage.

As the exposure instances increase, changing from episodic to more continuous and increasing from weeks to months to years, it is clear that too much exposure increases the likelihood of noncancer respiratory system damage or the risk of lung cancer, and thus we say DE at some level of chronic exposure poses a respiratory hazard for humans. Both human and animal studies provide evidence of this. But the human evidence specifically for diesel exhaust is not as clear as that from the well-controlled studies in test animals. As the total exposure over a lifetime increases, basic respiratory functions can be impaired, and there is a probability (i.e., risk) that lung tumors may appear later in life. Part of the permanent harm may be caused by the particle portion of the exhaust, part may be caused by the other inorganic/organic constituents on the particle or in the DE gases, or all of these may be interacting to influence the adverse outcome. With animal studies being conducted at high test exposures, and with the occupational human studies being somewhat lower in exposure but greater than ambient levels of DE, it is necessary to rationalize whether DE also poses a low-exposure hazard, whereas it is clear that at high exposure/doses it does. Plausible explanations supported by observations about adverse effects at higher doses are not matched with equal information about how effects may develop at low doses, and thus there is uncertainty about how to best estimate the low-dose hazards or risk. These questions are a current pursuit of health researchers. EPA also takes the position that chronic DE exposure, at high or low concentrations, is very likely to increase the hazard and risk of an adverse consequence.

Specific individuals inherently have varied susceptibility to these adverse outcomes, depending on whether they already have a weakened or compromised respiratory system, perhaps by smoking or having allergic or asthmatic symptoms. Although it is not demonstrated, one could hypothesize that episodic or frequent exposure of young children to DE could disproportionally increase their lifetime respiratory hazard or lifetime cancer risk, because damage early in life could increase their susceptibility, in addition to their having a longer period to accumulate exposure. Current data do not permit any more definitive explanations, nor is there a confident identification of additional human health hazards beyond those to the respiratory system.

What recommendations exist to protect human health?

This health assessment identifies the likely human health hazards and uses additional risk assessment tools to assist decision-makers in understanding what is important for protection of public health. These tools are in the form of concentration-based exposure-response relationships based on the identified hazard likelihood (i.e., respiratory damage or lung cancer). These relationships facilitate the rough estimation of acceptable/unacceptable exposures or health impacts. Use of these measures requires caution and recognition of the biological and risk assessment uncertainties that are present.

For the acute effects of DE exposure, there is no specific recommendation from this assessment for a concentration not to be exceeded in order to avoid acute effects, because of an absence of sufficient data. Clearly, if acute symptoms are noted one would want to remove oneself from the locale as soon as practicable, if for no other reason than personal comfort. As the level of exposure increases, the acute symptoms can become more annoying and be indicative of temporary impairment. With the inherent variability of susceptibility and sensitivity in the human population, it is not possible to judge the outcome of a specific exposure incident. The same statements could generally be made about exposure to gasoline exhaust and many other agents as well.

For the chronic effect hazards, EPA believes that for many people, keeping long-term exposures at or below 5 $\mu g/m^3$ of diesel particulate matter provides an adequate margin of safety for noncancer respiratory hazards. This level also includes a 10-fold margin to account for variability in the human population. This is not an absolute demarcation of acceptable versus unacceptable exposure, since an order-of-magnitude range of uncertainty is thought appropriate for this recommendation. For practical purposes, the belief is that as the long-term average exposure concentration exceeds this value, the likelihood of respiratory distress increases. The 5 $\mu g/m^3$ value comes from test animals who experienced respiratory distress at higher experimental exposures to which a margin of safety (e.g., uncertainty factor) and animal-to-human equivalence factors have been used to derive the 5 $\mu g/m^3$ level for humans. It was necessary to depend on animal studies because the human database was not robust enough. While children should not, a priori, be assumed to be protected by adult recommendations, at this time there is no separate recommendation for children, except for the general wisdom to minimize exposure as much as possible.

For carcinogenic hazard and risk of cancer over a lifetime, EPA is recommending that exposure be viewed as likely to pose a risk at low levels, as well as high levels, and is offering a crude range of cancer risks per unit of lifetime exposure in order to gauge the public health acceptability of exposures. The risk values provide an upper bound to the possible human risk, rather than a true estimate; the true estimate is undefinable and could be much lower. A range of risk estimators was provided because the available cancer data had too many uncertainties to justify the selection of one scientifically best estimate. The risk range is thought to bracket the upper limits of possible risk, and these values would not likely underestimate the true risk.

Assuming that DE is a cancer hazard for humans, EPA believes that the cancer risks for DE are not likely higher than 1×10^{-5} to 200×10^{-5} per $\mu g/m^3$ of diesel particulate. These values evolve from consideration of human occupational exposure-responses, several types of high-dose animal studies, and extrapolation to provide an appropriate estimate for low exposures. Extrapolation below the range of observation has uncertainty but is necessary from a public health perspective, because low-exposure cancer effects are often not detectable, yet low exposure hazards are expected for DE given our knowledge about the DE mixture components. Numerically, the risk estimates are the same as saying the probability of cancer could be, and is not likely higher than, 1/100,000 to 200/100,000 per microgram of diesel particulate matter per cubic meter of air ($\mu g/m^3$, an average particle concentration over a lifetime).

With exposure information, a risk assessor can make crude estimates of the highest possible impacts on a population, if such analysis is desirable. Under this type of evaluation, for an individual the development of cancer is a matter of chance. A person either gets cancer or doesn't by the end of their lifetime, but in the interim they have a probability (i.e., a risk) of getting cancer.

Nationally, the lifetime risk of being diagnosed with any type of cancer is about 1 in 4 (1/4), and as a cause of death is about 1 in 5 (1/5). Cancer of the lung runs about 1 in 12 for males and 1 in 19 for females.

As an example of how the crude risk estimations can be informative, at a hypothetical human average lifetime DE exposure of 2 μg/m^3, there would be little likelihood of noncancer respiratory hazard because this is less than 5 μg/m^3, whereas the cancer risks are not likely higher than 2 /100,000 (1 in 50,000) up to about 400/100,000 (1 in 250). At a concentration of 5 μg/m^3, which is still presumed protective for respiratory effects, there remains an upper-limit cancer risk of 5/100,000 (1 in 20,000) up to 1,000/100,000 (1/100). It should be noted that as these all of these risks are upper bound, the true risk is unlikely to be greater and may well be less.

Are there other important considerations of DE exposure?

Particulates (i.e, particulate matter, PM) are a prominent constituent in DE. Breathing nonspecific PM is a public health concern in its own right, as evidenced by EPA's 1997 Ambient Air Quality standards for PM. When present, DE plays a role in contributing to ambient PM, especially $PM_{2.5}$ (PM less than 2.5 um in diameter). Diesel particulates are small; more than 75% of them can be less than 1 μm, which means that EPA's new $PM_{2.5}$ standard provides another health-based reference point. DE particulates are potentially a more toxic fraction in a $PM_{2.5}$ mixture because the smaller DE particles (<1 μm) can be deposited deeper in the lung. Because of their small size they also have a large surface area per unit mass and carry a coating of organic compounds with them. Though diesel particulates are associated with a carcinogenic hazard, this is not indicated, per se, for ambient PM exposure.

Older diesel engines emit higher levels of nitrogen oxides (NO_x) than do gasoline engines, and NO_x is also an ambient urban contaminant that EPA seeks to reduce because of its influence on ozone formation, formation of nitrate PM, acid rain, and the eutrophication of coastal waters. Some new engine design is focused on reducing the NOx.

Those individuals who already carry a significant burden of particles in their lungs or have weakened respiratory systems (e.g., from allergies, asthma, or other respiratory system inflammation) could be at higher hazard/risk. These special population subgroups are difficult to enumerate, but they do exist. These same individuals might also be more sensitive to a number of insults, such as general PM or gasoline engine exhaust or smog.

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